Affiliated Genetics

2749 East Parleys Way, Suite 100
Salt Lake City, UT 84109
CLIA ID: 46D1077919

Affiliated Pharmarisk Cardiac Created for:

Patient:
HIPAA Compliant Fax:
Physician:
Address:

Collection Date:
Specimen Type:

Accession #:
Gender:
DOB:
Received Date:

Report Generated:

Key Test Findings

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Pharmacogenetic Results

	Assay	Results	Phenotype	Clinical Consequences
✓	ABCG2	421C>A CC	Normal Transporter Function	Consistent with a normal ABCG2 transporter function. The patient's risk for statin-induced adverse events is normal.
⚠	ANKK1/DRD2	DRD2:Taq1A AG	Altered DRD2 function	Consistent with a reduced dopamine receptor D2 function.
⚠	COMT	Val158Met AG	Intermediate COMT Activity	Consistent with a reduced catechol O-methyltransferase (COMT) function.
✓	CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility	Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid Metabolism occurs in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.
✓	CYP2B6	*1/*1	Normal Metabolizer	Consistent with a typical CYP2B6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
🚩	CYP2C19	*1/*17	Rapid Metabolizer	Consistent with a significant increase in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.
✓	CYP2C9	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
🚩	CYP2D6	*1/*1 XN	Rapid Metabolizer	Consistent with a significant increase in CYP2D6 activity. Potential risk for side effects or loss of efficacy with drug substrates.
⚠	CYP3A4	*1/*22	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
✓	CYP3A5	*3/*3	Poor Metabolizer	Consistent with a poor CYP3A5 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
⚠	OPRM1	A118G AA	Normal OPRM1 Function	Consistent with a normal OPRM1 receptor signaling efficiency induced by exogenous opioids. This is associated with a good analgesia following standard opioid doses and a poor response to naltrexone.
🚩	SLCO1B1	521T>C CC	Low Transporter Function	Consistent with a severely decreased SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is increased.
⚠	UGT2B15	*1/*2	Intermediate Metabolizer	Consistent with a moderately decreased UGT2B15 glucuronidation function. Potential risk for side effects with drug substrates.
🚩	VKORC1	-1639G>A A/A	High Warfarin Sensitivity	VKORC1 is the site of action of warfarin. The patient may require a substantial decrease in warfarin dose.

Cardiovascular/Thrombosis Risk Management

	Gene	Genotype	Phenotype	Clinical Consequences
✓	Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No Increased Risk of Thrombosis	Unless other genetic or circumstantial risk factors are present, the patient is not expected to have an increased risk for thrombosis.
🚩	MTHFR MTHFR	1298A>C AA 677C>T TT	Increased Risk of Hyperhomocysteinemia	The patient has a significantly reduced MTHFR function leading to mild to moderate hyperhomocysteinemia. This appears to be associated with an increased risk for venous thromboembolism.

✓	Apolipoprotein E	ε3/ε3	No Increased Risk of Hyperlipidemia/Atherosclerotic Vascular Disease	The patient has a normal APOE genotype and unless other genetic or circumstantial risk factors are present, the risk for hyperlipidemia/atherosclerotic vascular disease is not increased.

Cardiovascular/Thrombosis Risk Management

✓ **Thrombophilia**

No Increased Risk of Thrombosis

Unless other genetic and/or circumstantial risk factors are present (ex: smoking, obesity…), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.

Hyperhomocysteinemia

Increased Risk of Hyperhomocysteinemia

Testing total plasma homocysteine level may be beneficial. Hyperhomocysteinemia can be treated with nutritional supplementation.

✓ **Hyperlipidemia/Atherosclerotic Cardiovascular Disease**

No increased risk of hyperlipidemia/atherosclerotic vascular disease

No action is needed when a patient in normolipidemic.

Medication Guidance

Psychotropic Medications

Standard Precautions	Use With Caution	Consider Alternatives
Amphetamine (Adderall)	Bupropion (Wellbutrin)	Amitriptyline (Elavil)
Aripiprazole (Abilify)	Clozapine (Clozaril)	Atomoxetine (Strattera)
Clobazam (Onfi)	Dexmethylphenidate (Focalin)	Citalopram (Celexa)
Desvenlafaxine (Pristiq)	Diazepam (Valium)	Clomipramine (Anafranil)
Dextroamphetamine (Dexedrine)	Donepezil (Aricept)	Desipramine (Norpramin)
Duloxetine (Cymbalta)	Lorazepam (Ativan)	Doxepin (Silenor)
Fosphenytoin (Cerebyx)	Methylphenidate (Ritalin)	Escitalopram (Lexapro)
Gabapentin (Neurontin)	Naltrexone (Vivitrol)	Haloperidol (Haldol)
Galantamine (Razadyne)	Olanzapine (Zyprexa)	Imipramine (Tofranil)
Iloperidone (Fanapt)	Oxazepam (Serax)	Nortriptyline (Pamelor)
Lisdexamfetamine (Vyvanse)	Perphenazine (Trilafon)	Paroxetine (Paxil)
Mirtazapine (Remeron)	Pimozide (Orap)	Risperidone (Risperdal)
Paliperidone (Invega)	Tetrabenazine (Xenazine)	Trimipramine (Surmontil)
Phenytoin (Dilantin)		Venlafaxine (Effexor)
Pregabalin (Lyrica)		
Sertraline (Zoloft)		
Thioridazine (Mellaril)		
Vortioxetine (Brintellix)		

Cardiovascular Medications

Standard Precautions	Use With Caution	Consider Alternatives
Carvedilol (Coreg)	Atorvastatin (Lipitor)	Flecainide (Tambocor)
Fluvastatin (Lescol)	Clopidogrel (Plavix)	Metoprolol (Lopressor)
Irbesartan (Avapro)	Lovastatin (Mevacor)	Simvastatin (Zocor)
Nebivolol (Bystolic)	Mexiletine (Mexitil)	
Prasugrel (Effient)	Pitavastatin (Livalo)	
Propranolol (Inderal)	Pravastatin (Pravachol)	
Ticagrelor (Brilinta)	Propafenone (Rythmol)	
Timolol (Timoptic)	Rosuvastatin (Crestor)	
	Warfarin (Coumadin)	

Pain Medications

Standard Precautions	Use With Caution	Consider Alternatives
Buprenorphine (Butrans, Buprenex)	Carisoprodol (Soma)	Codeine (Codeine)
Celecoxib (Celebrex)	Dihydrocodeine (Synalgos-DC)	Tramadol (Ultram)
Cyclobenzaprine (Flexeril, Amrix)	Hydrocodone (Vicodin)	
Fentanyl (Actiq)	Oxycodone (Percocet)	
Flurbiprofen (Ansaid)	Tizanidine (Zanaflex)	
Hydromorphone (Dilaudid, Exalgo)		
Meperidine (Demerol)		
Methadone (Dolophine)		
Morphine (MS Contin)		
Oxymorphone (Opana, Numorphan)		
Piroxicam (Feldene)		
Tapentadol (Nucynta)		

Other Medications

Standard Precautions	Use With Caution	Consider Alternatives
Darifenacin (Enablex)	Dexlansoprazole (Dexilant)	Ondansetron (Zofran)
Fesoterodine (Toviaz)	Esomeprazole (Nexium)	
Glimepiride (Amaryl)	Lansoprazole (Prevacid)	
Glipizide (Glucotrol)	Omeprazole (Prilosec)	
Glyburide (Micronase)	Pantoprazole (Protonix)	
Metoclopramide (Reglan)	Voriconazole (Vfend)	
Mirabegron (Myrbetriq)		
Rabeprazole (Aciphex)		
Tacrolimus (Prograf)		
Tamsulosin (Flomax)		
Tolbutamide (Orinase)		
Tolterodine (Detrol)		

PharmaRisk™ Cardiac

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Test Details

Gene	Alleles Tested
ABCG2	421C>A, 376C>T
ANKK1/DRD2	DRD2:Taq1A
Apolipoprotein E	ε2, ε4
COMT	Val158Met
CYP1A2	*1C, *1D, *1F, *1K, *1L, *1V, *1W
CYP2B6	*4, *5, *6, *8, *9, *11, *18, *22, *28
CYP2C19	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *12, *17
CYP2C9	*2, *3, *4, *5, *6, *8, *10, *11, *12, *13, *15, *25, *27
CYP2D6	*2, *3, *4, *4M, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *18, *19, *20, *29, *35, *38, *41, *44, *56, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1B, *2, *3, *6, *12, *17, *22
CYP3A5	*1D, *2, *3, *3C, *5, *6, *7, *8, *9
Factor II	20210G>A
Factor V Leiden	1691G>A
MTHFR	1298A>C
MTHFR	677C>T
OPRM1	A118G
SLCO1B1	*5, *15
UGT2B15	*2
VKORC1	1542G>C, -1639G>A, 1173C>T

Methodology:

Testing is performed on DNA extracted from a buccal swab. Samples are genotyped using Taqman® allele discrimination assays. The assays detect alleles listed above, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Limitations:

The interpretations provided in this report are provided to assist health care providers, but they are not a treatment recommendation. Diagnosis and treatment remain the sole responsibility of the ordering physician. While the polymorphisms tested are important, other variants and mutations in these genes will not be detected. Mutations in other genes that could affect drug metabolism will not be detected. Non-genetic factors also affect metabolism. This test is not a substitute for clinical and therapeutic drug monitoring. This report does not address patient drug allergies or drug-drug interactions.

Signature:

Kenneth Ward M.D.

Date: 7/3/2014

CLIA FDA Statement:

This Laboratory Developed Test was developed and its performance characteristics determined by Affiliated Genetic, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing and has established and verified the test's accuracy. This test has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. These results are adjunctive to an ordering physician's diagnosis.

Appendix: Dosing Guidance

Amitriptyline (Elavil)

Increased Sensitivity to Amitriptyline (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing amitriptyline at standard dose and monitor the plasma concentrations of amitriptyline and nortriptyline to guide dose adjustments.

Amitriptyline (Elavil)

Non-Response to Amitriptyline (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or prescribe amitriptyline at increased dose and monitor the plasma concentration of amitriptyline and metabolites.

Atomoxetine (Strattera)

Non-Response to Atomoxetine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider prescribing atomoxetine with careful titration and monitoring for reduced efficacy. There is insufficient data to calculate dose adjustment. Or consider alternative drug such as methylphenidate.

Atorvastatin (Lipitor)

Altered Response to Atorvastatin (CYP3A4 *1/*22 Intermediate Metabolizer)

The genotype result indicates that the patient carries the CYP3A4*22 allele (this allele is associated with lower CYP3A4 enzyme activity). Preliminary studies have shown that patients carrying the CYP3A4*22 allele may achieve an optimal lipid control goal with lower atorvastatin dose requirements.

Atorvastatin (Lipitor)

Increased Myopathy Risk (SLCO1B1 521T>C CC Low Transporter Function)

The reduced SLCO1B1 function may result in elevated atorvastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high atorvastatin doses in this patient should be avoided. If atorvastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications and female gender.

Bupropion (Wellbutrin)

Decreased Response to Bupropion (ANKK1 DRD2:Taq1A AG Altered DRD2 function)

Smoking Cessation: The patient's genotype is associated with a positive response to nicotine replacement therapy and a lesser response to bupropion treatment.

Carisoprodol (Soma)

Altered Sensitivity to Carisoprodol (CYP2C19 *1/*17 Rapid Metabolizer)

There is insufficient data to allow calculation of dose adjustment and if carisodoprol is prescribed, it is recommended to use a lower dose and to carefully monitor the patient for side effects.

Citalopram (Celexa)

Insufficient Response to Citalopram (CYP2C19 *1/*17 Rapid Metabolizer)

The patient may not respond to usual doses. Monitor plasma concentration and increase dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.

Clomipramine (Anafranil)

Increased Sensitivity to Clomipramine (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing clomipramine at standard dose and monitor the plasma concentrations of clomipramine and desmethyl-clomipramine to guide dose adjustments.

Clomipramine (Anafranil)

Non-Response to Clomipramine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or prescribe clomipramine at increased dose and monitor the plasma concentration of clomipramine and desmethylclomipramine.

Clopidogrel (Plavix)

Increased Response to Clopidogrel (CYP2C19 *1/*17 Rapid Metabolizer)

Clopidogrel can be prescribed at standard label-recommended dosage. Individuals with the *17 allele may have an increased risk of bleeding while taking clopidogrel.

Clozapine (Clozaril)

Non-Response to Clozapine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility)

Smokers have a high risk for non-response and may require higher doses. There is an association between high clozapine doses and the risk of seizures, therefore careful monitoring is recommended during dosing adjustment. Smoking cessation will increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.

Codeine (Codeine)

Increased Response to Codeine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Greatly increased morphine levels are expected and the patient is at high risk of toxicity when taking codeine. Avoid prescribing codeine and consider an alternative opioid or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

Desipramine (Norpramin)

Non-Response to Desipramine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or prescribe desipramine at increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to desipramine and metabolites plasma concentrations and clinical response.

Dexlansoprazole (Dexilant)

Possible Insufficient Response to Dexlansoprazole (CYP2C19 *1/*17 Rapid Metabolizer)

Be alert to insufficient response and **consider dose increase**. There is insufficient data to allow calculation of dose adjustment.

Dexmethylphenidate (Focalin)

Decreased Response to Dexmethylphenidate (COMT Val158Met AG Intermediate COMT Activity)

The patient's genotype predicts a less optimal response to dexmethylphenidate. Dosage should be individualized according to the needs and responses of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Diazepam (Valium)

Altered Sensitivity to Diazepam (CYP2C19 *1/*17 Rapid Metabolizer)

There is insufficient data to allow calculation of dose adjustment when diazepam is prescribed. Monitor the response and adjust the dose accordingly or select an alternative drug.

Dihydrocodeine (Synalgos-DC)

Possible Altered Response to Dihydrocodeine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Increased conversion of dihydrocodeine to the more active metabolite dihydromorphine is expected in CYP2D6 rapid metabolizers. This may result in an exaggerated response. Adequate pain relief can be achieved by decreasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone) may also be considered if signs of overdose (excessive sleepiness, confusion, or shallow breathing) are reported.

Donepezil (Aricept)

Possible Altered Response to Donepezil (CYP2D6 *1/*1 XN Rapid Metabolizer)

When compared to a normal metabolizer, a rapid metabolizers has a 24% increase in donepezil clearance; the clinical significance of this increase is not well documented. Consider using a standard dosing regimen and adjust dosage in response to clinical response and tolerability.

Doxepin (Silenor)

Increased Sensitivity to Doxepin (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing doxepin at standard dose and monitor the plasma concentrations of doxepin and desmethyl-doxepin to guide dose adjustments.

Doxepin (Silenor)

Non-Response to Doxepin (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or increase doxepin dose by 100%. Adjust maintenance dose according to nordoxepin plasma concentrations.

Escitalopram (Lexapro)

Insufficient Reponse to Escitalopram (CYP2C19 *1/*17 Rapid Metabolizer)

Monitor plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.

Esomeprazole (Nexium)

Insufficient Response to Esomeprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 50-100% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 50-100%.

Flecainide (Tambocor)

Altered Response to Flecainide (CYP2D6 *1/*1 XN Rapid Metabolizer)

Titrate carefully and consider adjusting dose in response to plasma concentration and ECG monitoring OR consider alternative drug. Example of alternatives drugs not affected by CYP2D6 include: sotalol, disopyramide, quinidine and amiodarone.

Haloperidol (Haldol)

Non-Response to Haloperidol (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or prescribe haloperidol at standard dose and adjust dosage to achieve a favorable clinical response. Be alert to decreased haloperidol plasma concentrations.

Hydrocodone (Vicodin)

Possible Altered Response to Hydrocodone (CYP2D6 *1/*1 XN Rapid Metabolizer)

Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower hydrocodone doses. Other opioids not metabolized by CYP2D6 (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone) may also be considered if excessive side effects are reported.

Imipramine (Tofranil)

Increased Sensitivity to Imipramine (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing imipramine at standard dose and monitor the plasma concentrations of imipramine and desipramine to guide dose adjustments.

Imipramine (Tofranil)

Non-Response to Imipramine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or consider prescribing imipramine at an increased dose and then adjust dosage in response to imipramine and desipramine plasma concentrations.

Lansoprazole (Prevacid)

Insufficient Response to Lansoprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 200%.

Lorazepam (Ativan)

Possible Altered Response to Lorazepam (UGT2B15 *1/*2 Intermediate Metabolizer)

Lorazepam clearance may be reduced in this patient. However, there is insufficient evidence as to whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

Lovastatin (Mevacor)

Altered Response to Lovastatin (CYP3A4 *1/*22 Intermediate Metabolizer)

The genotype result indicates that the patient carries the CYP3A4*22 allele (this allele is associated with lower CYP3A4 enzyme activity). Preliminary studies have shown that patients carrying the CYP3A4*22 allele may achieve an optimal lipid control goal with lower lovastatin dose requirements.

Methylphenidate (Ritalin)

Decreased Response to Methylphenidate (COMT Val158Met AG Intermediate COMT Activity)

The patient's genotype predicts a less optimal response to methylphenidate. Dosage should be individualized according to the needs and responses of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

Metoprolol (Lopressor)

Possible Non-Responder to Metoprolol (CYP2D6 *1/*1 XN Rapid Metabolizer)

The patient may experience a decrease in the pharmacological effect when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol or prescribe metoprolol at a higher dose. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol or or prescribe metoprolol at a higher dose. If metoprolol is prescribed, titrate dose to a maximum of 250% of the normal dose in response to efficacy and adverse events.

Mexiletine (Mexitil)

Altered Response to Mexiletine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Because mexiletine plasma concentrations may be decreased, consider adjusting dose in response to mexiletine plasma concentration and ECG monitoring until a favorable response in achieved.

Naltrexone (Vivitrol)

Altered Response to Naltrexone (OPRM1 A118G AA Normal OPRM1 Function)

Treatment of alcohol dependence: the patient's has the wild-type genotype for OPRM1 that is associated with a poorer outcome with naltrexone therapy. Naltrexone-treated patients not carrying the 118A> G mutation, are less likely to respond to this drug and may have higher relapse rates than those who are carriers of this mutation.

Nortriptyline (Pamelor)

Non-Response to Nortriptyline (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or prescribe nortriptyline at increased dose and monitor the plasma concentration of amitriptyline and hydroxynortriptyline.

Olanzapine (Zyprexa)

Non-Response to Olanzapine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility)

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Smokers may be at risk for non-response at standard doses. Careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Omeprazole (Prilosec)

Insufficient Response to Omeprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 100-200% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 100-200%.

Ondansetron (Zofran)

Non-Response to Ondansetron (CYP2D6 *1/*1 XN Rapid Metabolizer)

A substantially decreased antiemetic effect has been reported in CYP2D6 rapid metabolizers. Consider prescribing an alternative drug not metabolized by CYP2D6 such as granisetron.

Oxazepam (Serax)

Possible Altered Response to Oxazepam (UGT2B15 *1/*2 Intermediate Metabolizer)

Oxazepam clearance may be reduced in this patient. However, there is insufficient evidence as to whether this change results in a significant clinical effect. Consider monitoring the patient for increased sedation and adjust dosing accordingly.

Oxycodone (Percocet)

Possible Altered Response to Oxycodone (CYP2D6 *1/*1 XN Rapid Metabolizer)

Increased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower oxycodone doses. Other opioids not metabolized by CYP2D6 (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone) may also be considered if excessive side effects are reported.

Pantoprazole (Protonix)

Insufficient Response to Pantoprazole (CYP2C19 *1/*17 Rapid Metabolizer)

- Helicobacter pylori eradication: increase dose by 400% and be alert to insufficient response.
- Other: be extra alert to insufficient response and consider dose increase by 400%.

Paroxetine (Paxil)

Non-Response to Paroxetine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or increase paroxetine dose and adjust dosage in response to efficacy.

Perphenazine (Trilafon)

Possible Non-Response to Perphenazine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Subjects with increased CYP2D6 function will metabolize perphenazine more rapidly which can result in sub-therapeutic drug concentrations. Consider a dose increase with close monitoring until a favorable response is achieved.

Pimozide (Orap)

Possible Non-Response to Pimozide (CYP2D6 *1/*1 XN Rapid Metabolizer)

There is insufficient data to calculate dose adjustment and if pimozide is prescribed at standard dosing, monitor response and be alert to reduced efficacy. Standard starting dose: 1 to 2 mg/day (adult) or 0.05 mg/kg/day (children) - Doses may be increased to a maximum of 10 mg/day or 0.2 mg/kg/day.

Pitavastatin (Livalo)

Increased Myopathy Risk (SLCO1B1 521T>C CC Low Transporter Function)

The reduced SLCO1B1 function may result in elevated pitavastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high pitavastatin doses in this patient should be avoided. If pitavastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications and female gender.

Pravastatin (Pravachol)

Increased Myopathy Risk (SLCO1B1 521T>C CC Low Transporter Function)

The reduced SLCO1B1 function may result in elevated pravastatin plasma levels. Because the risk of myopathy increases in patients with high statin plasma levels, the use of high pravastatin doses in this patient should be avoided. If pravastatin is used in this patient, a closer monitoring of serum creatine kinase and liver function is recommended. Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, comedications and female gender.

Propafenone (Rythmol)

Altered Response to Propafenone (CYP2D6 *1/*1 XN Rapid Metabolizer)

There is insufficient data to allow calculation of dose adjustment. Titrate carefully and adjust dose in response to plasma concentration and ECG monitoring. OR consider alternative drug such as sotalol, disopyramide, quinidine and amiodarone.

Risperidone (Risperdal)

Non-Response to Risperidone (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or prescribe risperidone and be extra alert to insufficient response and adjust dosage in response to clinical response and adverse events.

Rosuvastatin (Crestor)

Increased Myopathy Risk (SLCO1B1 521T>C CC ABCG2 421C>A CC)

The patient does not carry a polymorphism in the ABCG2 gene that is associated with a higher rosuvastatin plasma exposure. The patient carries a polymorphism in the SLCO1B1 gene that is associated with an increased risk of myopathy. Rosuvastatin plasma concentrations are expected to increase and the patient's risk of rosuvastatin-induced myopathy is elevated. Other factors that may increase this risk further include: uncontrolled hypothyroidism, renal impairment, diabetes and comedications with ABCG2 or SLCO1B1 inhibitors. Patient's age is 20-60 or > 60 years; maximum recommended dose range to reduce the risk of high statin exposure: 20 mg/day. Start with usual doses 10-20 mg/day or 5 mg/day in Asian patients.

Simvastatin (Zocor)

High Myopathy Risk (SLCO1B1 521T>C CC Low Transporter Function)

Simvastatin plasma concentrations are expected to be elevated. **1-Consider avoiding simvastatin** and prescribe an alternative statin or an other hypolipidemic drug or 2-Consider prescribing simvastatin at a lower starting dose (20 mg/day). Routine Creatine Kinase (CK) monitoring is also advised. **The FDA recommends against the 80 mg daily dose.** Although the association between the SLCO1B1 521C>T variant and myopathy risk is not clearly established for other statins such as atorvastatin, pitavastatin, rosuvastatin and pravastatin, caution is advised if high doses of these statins are used in this patient. Fluvastatin plasma levels are not affected by the SLCO1B1 521C>T variant.

Tetrabenazine (Xenazine)

Unknown Sensitivity to Tetrabenazine (CYP2D6 *1/*1 XN Rapid Metabolizer)

There is insufficient data to calculate dose adjustment and if tetrabenazine is prescribed, individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 rapid metabolizers is not defined. The maximum daily dose in normal metabolizers is 100 mg with a maximum single dose of 37.5 mg.** If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.

Tizanidine (Zanaflex)

Possible Non-Response to Tizanidine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility)

There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation, therefore careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have quit smoking.

Tramadol (Ultram)

Increased Response to Tramadol (CYP2D6 *1/*1 XN Rapid Metabolizer)

The patient is at high risk of toxicity when taking tramadol at standard dosing. Consider reducing tramadol dose by 30%. Careful monitoring for side effects and weekly titration are recommended. If toxicity, consider alternative opioids other than codeine or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

Trimipramine (Surmontil)

Increased Sensitivity to Trimipramine (CYP2C19 *1/*17 Rapid Metabolizer)

Consider an alternative drug or consider prescribing trimipramine at standard dose and monitor the plasma concentrations of trimipramine and desmethy-ltrimipramine to guide dose adjustments.

Trimipramine (Surmontil)

Non-Response to Trimipramine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or consider prescribing trimipramine at an increased dose and then adjust dosage in response to trimipramine plasma concentrations.

Venlafaxine (Effexor)

Non-Response to Venlafaxine (CYP2D6 *1/*1 XN Rapid Metabolizer)

Consider alternative drug or increase venlafaxine dose to a maximum of 150% of the normal dose and monitor venlafaxine and O-desmethylvenlafaxine plasma concentrations.

Voriconazole (Vfend)

Non-response to Voriconazole (CYP2C19 *1/*17 Rapid Metabolizer)

Voriconazole plasma concentrations may be low when standard dosage is used, increasing the risk of loss of response and effectiveness. Closely monitor voriconazole plasma concentrations and adjust the dose accordingly.

Warfarin (Coumadin)

Moderate Sensitivity to Warfarin (CYP2C9 *1/*1 VKORC1 -1639G>A A/A)

Initiation Therapy: a dose decrease may be required. Consider using the following warfarin dose range provided in the FDA -approved label: **3-4 mg/day.** OR consider using a personalized dose calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 4-5 days.

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Prescription Alert

DOB

This individual has been tested for gene variants that may affect medications prescribed.

GENE	RESULT
ABCG2	Normal Transporter Function
ANKK1	Altered DRD2 function
COMT	Intermediate COMT Activity
CYP1A2	Normal Metabolizer - Higher Inducibility
CYP2B6	Normal Metabolizer
CYP2C19	Rapid Metabolizer
CYP2C9	Normal Metabolizer
CYP2D6	Rapid Metabolizer
CYP3A4	Intermediate Metabolizer
CYP3A5	Poor Metabolizer
OPRM1	Normal OPRM1 Function
SLCO1B1	Low Transporter Function
UGT2B15	Intermediate Metabolizer
VKORC1	High Warfarin Sensitivity

Healthcare Providers: For up-to-date information concerning the impact of these genetic tests on drug precribing by may consult the PharmGKB database:

www.pharmgkb.org

Note:This patient has also been tested for common variants in the Factor II, Factor V, MTHFR, and ApoE genes.These results are available on the patient's medical records.